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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1648	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/766,528	SALZWEDEL ET AL.	
	Examiner	Art Unit	
	Louise Humphrey, Ph.D.	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,9,10,12,13 and 82-86* is/are pending in the application.

4a) Of the above claim(s) *85 and 86* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,9,10,12,13 and 82-84* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/31/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 31 October 2007 has been entered.

Applicants' request for interview has been noted. However, Applicants did not indicate what issues they desire to discuss at the interview. An interview should be had only when the nature of the case is such that the interview could serve to develop and clarify specific issues and lead to a mutual understanding between the examiner and the applicant, and thereby advance the prosecution of the application. MPEP §713. Since there are outstanding rejections in this case and Applicants have already responded to the rejections, an interview at this time does not advance the prosecution of the application. Therefore, an interview is not granted

Claims 8, 11 and 14-81 have been cancelled. Claims 85 and 86 have been added and present a new invention that is separate from the election invention because claims 85 and 86 are directed a method administering an entirely different product, *i.e.*, a derivative of oleanolic acid, pomolic acid, ursolic acid, or platonic acid, which is patentably distinct from the derivative of betulin or betulinic acid used in the elected invention. Even though Applicants allege that these are all triterpenes, there are many functional groups modifying the fused ring structure and diversifying the functional

characteristics to render the two groups of derivatives patently distinct and non-coextensive in searches. Therefore, claims 85 and 86 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected method invention. Claims 1-7, 9, 10, 12, 13 and 82-86 are pending. Claims 1-7, 9, 10, 12, 13 and 82-84 are currently examined.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. §112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The rejection of claims 1-7, 9, 10 and 82-84 under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement is **maintained and extended** to claim 12. Applicants' arguments have been fully considered and are not persuasive.

Claims 1-7, 9, 10, 12 and 82-84 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The instant claims are drawn to a method of treating HIV-1 infection in a patient, comprising administering to a patient in need thereof a compound that inhibits p25 (CA-SP1) processing to p24 (CA), wherein the HIV-1 does not contain a mutation encoding a substitution or deletion of one amino acid in SP1 or in the region of the CA-SP1 cleavage site that decreases inhibition of said processing by 3-O-(3',3'-dimethylsuccinyl) betulinic acid (DSB) and wherein said compound is a derivative of betulin or betulinic acid, or a pharmaceutically acceptable salt of said derivative.

The factors considered in the Written Description requirement are (1) level of skill and knowledge in the art, (2) partial structure, (3) physical and/or chemical properties, (4) functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the (5) method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient." M.P.E.P. §2163.

M.P.E.P. § 2163 further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." M.P.E.P. § 2163 also states that for a generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. If the genus has a substantial variance, the disclosure must

describe a sufficient variety of species to reflect the variation within that genus. See M.P.E.P. § 2163. Although the M.P.E.P. does not define what constitutes a sufficient number of representative species, the courts have indicated what do not constitute a representative number of species to adequately describe a broad genus. In *Gostelli*, the courts determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. *In re Gostelli,* 872, F.2d at 1012, 10 USPQ2d at 1618.

In the instant case, the claims encompass two broad genera: (1) a mutation of one amino acid in SP1 or CA-SP1 cleavage site that decreases inhibition of said processing by DSB; and (2) a derivative of betulin or betulinic acid. The claimed "mutation" reads on any single amino acid substitution or deletion in SP1 or the CA-SP1 cleavage site in any strain of HIV-1. A "derivative" reads on any compound with unlimited number and kinds of modification from the prototype structure of betulin or betulinic acid. The claimed genera of the "singe mutation" and the "derivative" are not adequately described in the specification.

The specification only discloses two single amino acid substitutions on page 12, in paragraph [0046] of the specification. A364V (SEQ ID NO:2) and A366V (SEQ ID NO:3) were identified in the DSB-resistant isolates when compared to the wild type sequence of HIV-1 s NL4-3 and RF (page 10, paragraph [0036], legend of Figure 4). No single deletions were disclosed anywhere in the specification. Therefore, the specification does not present a sufficient number of representative species that encompass the genus of DSB-resistant single-amino-acid substitutions or deletions.

The specification only provides description for one HIV-1 Gag p25 processing inhibitor compound, 3-O-(3',3'- dimethylsuccinyl) betulinic acid (DSB). See specification page 11, paragaraph [0044], and pages 50-60, Example 1-8. Although the specification presents examples of the derivatives of beulinic acid and betulin on page 30, paragraph [0084], there is no correlation between the inhibition function and the derivative structure beyond the DSB disclosed in the examples in the specification. Neither does the specification identify any partial structure of the claimed "derivative" that must be conserved to retain the function of inhibition of HIV-1 Gag p25 processing. Therefore, the specification lacks sufficient variety of species to reflect this variance in the genus. Applicants have not conveyed with reasonable clarity to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed genera of DSB-resistant single mutations and betulin or betulinic acid derivatives.

Applicants argue that these recited compounds are structurally related in that they are all triterpenes (also known in the prior art as triterpenoids), which share a common core structure in their backbone of four fused six-carbon rings. However, a triterpene is not a required structural feature for the recited "derivative of betulin or betulinic acid" in the claims. More importantly, the specification does not correlate the triterpene structure with the function of inhibition of HIV-1 Gag p25 processing. Furthermore, the instant claims do not limit the "derivative" to a triterpenoid. Nor does the subgenus of triterpene encompass the entire genus of derivatives. Therefore, the instant claims do not meet the written description requirement.

The rejection of claims 1-7, 9, 10 and 82-84 under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement is **maintained and extended** to claims 12 and 13 because the specification, while being enabling for treating non-DSB-resistant HIV-1 infection in a patient with DSB, does not reasonably provide enablement for treating HIV-1 with any other derivative of betulin or betulinic acid.

In making a determination as to whether an application has met the requirements for enablement under 35 U.S.C. 112 ¶ 1, the courts have put forth a series of factors (MPEP §2164.01(a)). See, *In re Wands*, 8 USPQ2d 1400, at 1404 (CAFC 1988); and *Ex Parte Forman*, 230 U.S.P.Q. 546 (BPAI 1986). The factors that may be considered include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *Id.* While it is not essential that every factor be examined in detail, those factors deemed most relevant should be considered.

The instant claims are drawn to a method of treating HIV-1 infection in a patient, comprising administering to a patient in need thereof a compound that inhibits p25 (CA-SP1) processing to p24 (CA), wherein the HIV-1 does not contain a mutation encoding a substitution or deletion of one amino acid in SP1 or in the region of the CA-SP1 cleavage site that decreases inhibition of said processing by 3-O-(3',3'-dimethylsuccinyl) betulinic acid (DSB) and wherein said compound is a derivative of betulin or betulinic

acid, or a pharmaceutically acceptable salt of said derivative. The nature of the invention is an HIV-1 treatment with a small molecule chemical compound that inhibits HIV-1 Gag p25 (CA-SP1) processing to p24 (CA). The claims read on a genus of unspecified compounds that are derived from betulin or betulinic acid. The claims are of excessive breadth and encompass any given putative anti-HIV compound without providing any meaningful structural limitations concerning that derivative. The claims encompass treatment of all clades and subtypes of non-DSB-resistant HIV-1 in a patient. The disclosure simply fails to support such breadth in the claim language.

The disclosure fails to provide sufficient working embodiments that meet the claimed limitations. While there are cell culture examples disclosed for the single species of by DSB in isolated peripheral blood mononuclear cells (PBMC) (Example 1-4), H9 cells (Example 5 and 7) and HeLa cells (Example 6), this compound does not represent all other betulin derivatives that fall within the scope of the invention. There are no other working examples of the claimed derivatives of betulin or betulinic acid. No *in vivo* working example of any betulin derivative is disclosed in the specification.

The specification provides no guidance regarding practice of the claimed method. The amount of direction is limited to a cell culture assay to determine the inhibitory effect of DSB on HIV maturation (spec. pages 53-54, Example 3, ¶159). First of all, there is no structural guidance to the broad genus of unspecified derivatives. In other words, the specification fails to disclose which chemical structures are critical for binding to Gag p25 (CA-SP1) and which structures are required for inhibiting the p25 processing to p24. Thus, the specification is no more than an undue invitation by the

applicant to further experimentation to identify putative HIV maturation inhibitors and determine their structures. Second, there is no teaching about the therapeutic properties such as the binding specificity, selectivity and affinity, oral bioavailability, cellular uptake, toxicity, lethal dose, and side effects. Lastly, there is no test to determine the efficacy and resistance of the claimed genus of derivatives to confirm the cell culture inhibitory results. There is not even a test to determine the cytopathic effect and the resistance of the claimed genus of derivatives. An *in vitro* testing is, at most, a useful tool for screening potential anti-viral agents but is not predictive of *in vivo* effectiveness. *Ex parte Balzarini* (BdPat App&Int) 21 USPQ2d 1892. One skilled in the art would not associate successful *in vitro* testing results with successful *in vivo* AIDS treatment without any knowledge of the pharmacokinetic profile, therapeutic and/or prophylactic effect in a patient. There is no evidence that shows any correlation of the *in vitro* activity with *in vivo* efficacy vis-a-vis the high level of unpredictability of this art. Therefore, the disclosure does not correlate with treating HIV in a patient.

It has been well known in the prior art (Gait, 1995) that the development of suitable HIV-1 therapeutics has been an arduous and empirical process, often ending in failure. This is due to a number of factors: (1) failure to understand the molecular determinants modulating many viral protein and host cell factor interactions; (2) failure of *in vitro* tissue culture studies and *in vivo* animal models to adequately predict clinical efficacy; (3) failure of many compounds to have acceptable pharmacological profiles despite initial favorable *in vitro* and *in vivo* activities; and (4) failure of related structural analogs to function in the desired manner, which provides further evidence of the

specificity of these molecular interactions. The challenges of developing efficacious anti-HIV agents are best summarized by Gait and Karn (1995) who state in the Conclusions (p.37): There can be few tasks in biotechnology that are more challenging than designing antiviral drugs. All of the protease inhibitors that have entered into clinical trials are potent inhibitors of HIV-1 replication in cell culture, and exhibit remarkable selectivity for the viral enzyme. Unfortunately, early protease inhibitors tended to suffer from problems of short serum half-life, poor availability and rapid clearance. As these pharmacokinetic problems have been addressed and solved, new difficulties have emerged from the resultant clinical experience, such as sequestration of the drug by serum proteins, drug resistance and uneven distribution throughout the body. Since these types of problems are unpredictable, it remains necessary to take into account the pharmacological parameters in any drug development programme at the earliest possible stage.

The art of HIV treatment in a patient is highly unpredictable because the effect of antiretroviral treatment appears to change due to pharmacokinetic variation, fluctuating adherence, the emergence of drug resistant mutations and/or other factors. Inadequate drug concentrations can result from a number of factors including non-adherence, pharmacokinetics, and lack of drug potency. In addition, anatomical sanctuary sites may exist where drug concentrations do not achieve adequate levels despite apparent therapeutic serum drug concentrations. HIV replication can occur in such settings, and the selective pressure of antiretroviral therapy leads to the emergence of HIV harboring drug-resistant mutations. Therefore, it is highly unpredictable to determine *in vivo*

efficacy by extrapolating from *in vitro* data. For determining *in vivo* efficacy, one skilled in the art has to address many highly unpredictable factors such as serum half-life, bioavailability, serum drug sequestration, clearance of the drugs themselves (Gait, 1995, page 437), cellular uptake, transport, metabolic activation, cell-, tissue-, and organ-specific toxicity (Lee, 2003, page 14713), all of which affect the concentration of the active form of the drugs at the site of action.

"Experimentation must not require ingenuity beyond that to be expected of one of ordinary skill in the art." See *Fields v. Conover*, 443 F.2d 1386, 170 USPQ 276 (CCPA 1970). In the instant case, a derivative of a betulin or betulini acid as a HIV-1 therapeutic is not considered routine in the art. The disclosure fails to address any of the aforementioned caveats in the development of an antiviral agent hence the experimentation left to those skilled in the art is undue or unreasonable under the circumstances.

For the reasons discussed above, it would require undue and unpredictable experimentation for one skilled in the art to use the claimed method.

Applicants argue that the Amendment and Reply filed on July 18, 2007 presented evidence that PA-457 (DSB) and the analog, PA-040 (DSD), have entered into FDA-approved clinical trials for treatment of HIV-1 infection. However, these two compounds are not representative of all the derivatives of betulin or betulinic acid and therefore are not predictive of the Gag inhibition effectiveness of any other derivatives of betulin or betulinic acid. Therefore, the evidence submitted by Applicants is not commensurate in

scope with the claimed invention. Further, Applicants' argument regarding the triterpenes is not germane to the issue because "triterpenes" is never a claim limitation.

NEW REJECTION

Claims 1-7, 9, 10, 12 and 82-84 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 12 recite a "derivative" of two specific compounds. The word "derivative" is vague because it is unclear what structural modifications to betulin or betulinic acid are permissible as a "derivative" yet retains the desired function of inhibiting Gag p25 processing to p24 in an HIV-1 that does not contain a mutation encoding a substitution or deletion of one amino acid in SP1 or in the CA-SP1 cleavage site that confers resistance to DSB.

Claims 2-7, 9, 10, and 82-84 are rejected for depending from an indefinite claim.

Correspondence

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic

Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louise Humphrey, Ph.D. whose telephone number is 571-272-5543. The examiner can normally be reached on Mon-Fri, 9:30 am - 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell, can be reached at 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Jeffrey Parkin, Ph.D.
Primary Examiner
01 February 2008

Louise Humphrey, Ph.D.
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